CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040095

Trade Name : HEPARIN SODIUM INJ USP

Generic Name: Heparin Sodium Injection USP 10,000u/ml 1ml

Sponsor : Sanofi Winthrop, Inc.

Approval Date: July 26, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040095

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040095

APPROVAL LETTER

ANDA 40-095

JUL 26 1996

Sanofi Winthrop, Inc.
Attention: Gregory M. Torre, Ph.D., J.D.
90 Park Avenue
New York, NY 10016

Dear Sir:

This is in reference to your abbreviated new drug application dated December 17, 1993, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Heparin Sodium Injection USP, 10,000 Units/mL, 1 mL fill in 2 mL vial.

Reference is also made to your amendment dated May 17, 1993.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Heparin Sodium Injection USP, 10,000 Units/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Heparin Sodium Injection, 10,000 Units/mL of Wyeth Ayerst Laboratories, Inc.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

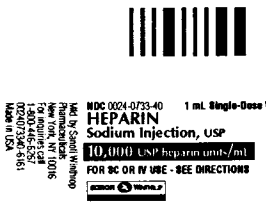
/S/ 7-26-96

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040095

FINAL PRINTED LABELING



APPROVED JUL 26 1996

PMS PROC. BLACK CV
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Sterile Aqueous Injection

Heparin Sodium Injection, USP

25 Single-Dose Vials 1 mL

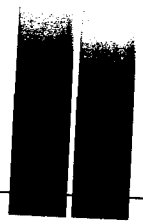
10,000 USP heparin units/mL

Each mL of Preservative-Free Heparin Sodium Injection contains 10,000 USP heparin units of heparin sodium derived from porcine intestinal mucosa in Water for Injection. The pH is adjusted between 5.0 to 7.5 with hydrochloric acid or sodium hydroxide as required.
For usual dose and route of administration, see package insert.

Do not use if solution is discolored or contains a precipitate. Discard unused portion after initial use.
Store at controlled room temperature 15°C to 30°C (59°F to 86°F). Do not freeze.

sanofi WINTHROP

Manufactured by Sanofi Winthrop Pharmaceuticals
New York, NY 10016 Made in USA
For inquiries call 1-800-446-6267



H-797 NDC 0024-0733-40 25 Single-Dose Vials 1 mL

Heparin Sodium Injection, USP

10,000 USP heparin units/mL

sanofi WINTHROP

H-797 NDC 002

Heparin Sc

10,000 USP he

FOR SC OR IV USE

Caution: Federal law prohibits

sanofi WINTHR

sanofi WINTHROP

10,000 USP heparin units/mL

Heparin Sodium Injection, USP

H-797 NDC 0024-0733-40 25 Single-Dose Vials 1 mL

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APPROVED

JUL 26 1996

25 Single-Dose Vials 1 mL

ıjection, USP

prescription.

H-797 NDC 0024-0733-40 25 Single-Dose Vials 1 mL

Heparin Sodium Injection, USP

10,000 USP heparin units/mL

sanofi WINTHROP

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Frequently, a dose of 300 units of heparin sodium per kilogram of body weight is used for procedures estimated to last less than 60 minutes; or 400 units per kilogram for those estimated to last longer than 60 minutes.

Low-Dose Prophylaxis of Postoperative Thromboembolism

A number of well-controlled clinical trials have demonstrated that low-dose heparin prophylaxis, given just prior to and after surgery, will reduce the incidence of postoperative deep-vein thrombosis in the legs (as measured by the I-125 fibrinogen technique and venography) and of clinical pulmonary embolism. The most widely used dosage has been 5,000 units 2 hours before surgery and 5,000 units every 8 to 12 hours thereafter for 7 days or until the patient is fully ambulatory, whichever is longer. The heparin is given by deep, subcutaneous injection in the arm or abdomen with a fine needle (25- to 26-gauge) to minimize tissue trauma. A concentrated solution of heparin sodium is recommended. Such prophylaxis should be reserved for patients over 40 undergoing major surgery. Patients with bleeding disorders, those having neurosurgery, spinal anesthesia, eye surgery, or potentially sanguineous operations should be excluded, as well as patients receiving oral anticoagulants or platelet-active drugs (see WARNINGS). The value of such prophylaxis in hip surgery has not been established. The possibility of increased bleeding during surgery or postoperatively should be borne in mind. If such bleeding occurs, discontinuance of heparin and neutralization with protamine sulfate is advisable. If clinical evidence of thromboembolism develops despite low-dose prophylaxis, full therapeutic doses of anticoagulants should be given unless contraindicated. All patients should be screened prior to heparinization to rule out bleeding disorders, and monitoring should be performed with appropriate coagulation tests just prior to surgery. Coagulation-test values should be normal or only slightly elevated. There is usually no need for daily monitoring of the effect of low-dose heparin in patients with normal coagulation parameters.

Extracorporeal Dialysis Use

Follow equipment manufacturers' operating directions carefully.

Blood Transfusion

Addition of 400 to 600 USP units per 100 mL of whole blood is usually employed to prevent coagulation. Usually, 7500 USP units of heparin sodium are added to 100 mL of 0.9% Sodium Chloride Injection, USP (or 75,000 USP units per 1,000 mL of 0.9% Sodium Chloride Injection, USP,) and mixed, and from this sterile solution, 6 mL to 8 mL are added per 100 mL of whole blood.

Laboratory Samples

Addition of 70 to 150 units of heparin sodium per 10 mL to 20 mL sample of whole blood is usually employed to prevent coagulation of the sample. Leukocyte counts should be performed on heparinized blood within two hours after addition of the heparin. Heparinized blood should not be used for isoagglutinin, complement,. erythrocyte fragility tests or platelet counts.

PARENTERAL DRUG PRODUCTS SHOULD BE INSPECTED VISUALLY FOR PARTICULATE MATTER AND DISCOLORATION PRIOR TO ADMINISTRATION, WHENEVER SOLUTION AND CONTAINER PERMIT. SLIGHT DISCOLORATION DOES NOT ALTER POTENCY.

HOW SUPPLIED

Heparin Sodium Injection, USP, Preservative Free is supplied as follows:

10,000 USP heparin Units/mL (1 mL fill in 2 mL cartridge).
Carpuject® sterile cartridge unit (25-gauge, 5/8 inch needle),
box of 10 (NDC 0024-0733-02); bin of 50 (NDC 0024-0733-12).

10,000 USP heparin Units/mL (1 mL fill in 2 mL single-dose vials),
box of 25 (NDC 0024-0733-40).

7,500 USP heparin Units/0.75 mL (0.75 mL fill in 2 mL cartridge).
CARPUJECT sterile cartridge unit (25-gauge, 5/8 inch needle),
box of 10 (NDC 0024-0733-04).

5,000 USP heparin Units/0.5 mL (0.5 mL fill in 2 mL cartridge).
CARPUJECT sterile cartridge unit (25-gauge, 5/8 inch needle),
box of 10 (NDC 0024-0733-05); bin of 50 (NDC 0024-0733-15).

2,500 USP heparin Units/0.25 mL (0.25 mL fill in 2 mL cartridge).
CARPUJECT sterile cartridge unit (25-gauge, 5/8 inch needle),
box of 10 (NDC 0024-0733-03).

Heparin Sodium Injection, USP, is supplied as follows:

5,000 USP heparin Units/mL (1 mL fill in 2 mL cartridge).
CARPUJECT sterile cartridge unit (25-gauge, 5/8 inch needle),
box of 10 (NDC 0024-0793-02); bin of 50 (NDC 0024-0793-12).

Store at controlled room temperature, 15° C to 30° C (59° F to 86° F).
Do not freeze.

Discard unused portion after initial use.

sanofi WINTHROP

Manufactured by Sanofi Winthrop Pharmaceuticals
New York, NY 10016

Printed in USA Revised May 1996

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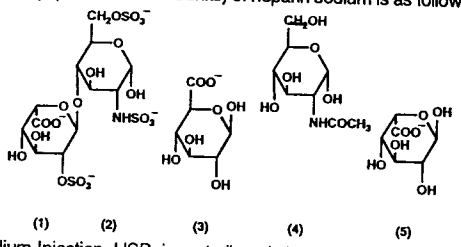
HEPARIN SODIUM INJECTION, USP

DESCRIPTION

Heparin is a heterogenous group of straight-chain anionic mucopolysaccharides, called glycosaminoglycans, having anticoagulant properties. Although others may be present, the main sugars occurring in heparin are: (1) α L-iduronic acid 2-sulfate, (2) 2-deoxy-2-sulfamino-α-D-glucose 6-sulfate, (3) β-D-glucuronic acid, (4) 2-acetamido-2-deoxy-α-D-glucose, and (5) α-L-iduronic acid. These sugars are present in decreasing amounts, usually in the order (2)> (1)> (4)> (3)> (5), and are joined by glycosidic linkages, forming polymers of varying sizes. Heparin is strongly acidic because of its content of covalently linked sulfate and carboxylic acid groups. In heparin sodium, the acidic protons of the sulfate units are partially replaced by sodium ions. The structural formula (representative subunits) of heparin sodium is as follows:



(1) (2) (3) (4) (5)

Heparin Sodium Injection, USP, is a sterile solution of heparin sodium derived from porcine intestinal mucosa, standardized for anticoagulant activity. It is to be administered by intravenous or deep subcutaneous routes. The potency is determined by a biological assay using a USP reference standard based on units of heparin activity per milligram.

Carpuject® sterile cartridge unit contains a sterile solution of Heparin Sodium Injection, USP. Each mL contains 5,000 USP heparin units of heparin sodium and benzyl alcohol 1% as a preservative, in Water for Injection. The pH is adjusted between 5.0 to 7.5 with hydrochloric acid or sodium hydroxide.

Each mL of Preservative-Free Heparin Sodium Injection contains 10,000 USP heparin units in Water for Injection. The pH is adjusted between 5.0 to 7.5 with hydrochloric acid or sodium hydroxide as required.

CLINICAL PHARMACOLOGY

Heparin inhibits reactions that lead to the clotting of blood and the formation of fibrin clots both *in vitro* and *in vivo*. Heparin acts at multiple sites in the normal coagulation system. Small amounts of heparin in combination with antithrombin III (heparin cofactor) can inhibit thrombosis by inactivating activated Factor X and inhibiting the conversion of prothrombin to thrombin. Once active thrombosis has developed, larger amounts of heparin can inhibit further coagulation by inactivating thrombin and preventing the conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin stabilizing factor.

Bleeding time is usually unaffected by heparin. Clotting time is prolonged by full therapeutic doses of heparin; in most cases, it is not measurably affected by low doses of heparin.

Peak plasma levels of heparin are achieved 2 to 4 hours following subcutaneous administration, although there are considerable individual variations. Loglinear plots of heparin plasma concentrations with time, for a wide range of dose levels, are linear which suggest the absence of zero order processes. The liver and reticulo-endothelial system are the sites of biotransformation. The biphasic elimination curve, a rapidly declining alpha phase ($t_{1/2}$ = 10 min.), and after the age of 40 a slower beta phase, indicates uptake in organs. The absence of a relationship between anticoagulant half-life and concentration half-life may reflect factors such as protein binding of heparin.

Heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots.

INDICATIONS AND USAGE

Heparin sodium injection is indicated for anticoagulant therapy in prophylaxis and treatment of venous thrombosis and its extension; in a low-dose regimen for prevention of postoperative deep venous thrombosis and pulmonary embolism in patients undergoing major abdomino-thoracic surgery who are at risk of developing thromboembolic disease (see DOSAGE AND ADMINISTRATION); for prophylaxis and treatment of pulmonary embolism; in atrial fibrillation with embolization; for diagnosis and treatment of acute and chronic consumptive coagulopathies (disseminated intravascular coagulation); for prevention of clotting in arterial and cardiac surgery; and for prophylaxis and treatment of peripheral arterial embolism.

Heparin may also be employed as an anticoagulant in blood transfusions, extracorporeal circulation, dialysis procedures, and in blood samples for laboratory purposes.

CONTRAINDICATIONS

Heparin sodium should not be used in patients:

- with severe thrombocytopenia;
- in whom suitable blood-coagulation tests—e.g., the whole-blood clotting time, partial thromboplastin time, etc.—cannot be performed at appropriate intervals (this contraindication refers to full-dose heparin; there is usually no need to monitor coagulation parameters in patients receiving low-dose heparin);
- with an uncontrollable active bleeding state (see WARNINGS), except when this is due to disseminated intravascular coagulation.

WARNINGS

Heparin is not intended for intramuscular use.

Hypersensitivity

Patients with documented hypersensitivity to heparin should be given the drug only in clearly life-threatening situations.

Hemorrhage

Hemorrhage can occur at virtually any site in patients receiving heparin. An unexplained fall in hematocrit, fall in blood pressure, or any other unexplained symptom should lead to serious consideration of a hemorrhagic event.

Heparin sodium should be used with extreme caution in disease states in which there is increased danger of hemorrhage. Some of the conditions in which increased danger of hemorrhage exist are:

- Cardiovascular—Subacute bacterial endocarditis. Severe hypertension.
- Surgical—During and immediately following (a) spinal tap or spinal anesthesia or (b) major surgery, especially involving the brain, spinal cord, or eye.
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Coagulation Testing

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Manufactured by Sanofi Winthrop Pharmaceuticals
New York, NY 10016

Printed in USA Revised May 1996

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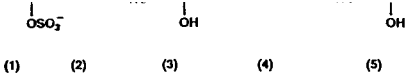

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- Hematologic—Conditions associated with increased bleeding tendencies, such as hemophilia, thrombocytopenia, and some vascular purpuras.
- Gastrointestinal—Ulcerative lesions and continuous tube drainage of the stomach or small intestine.
- Other—Menstruation, liver disease with impaired hemostasis.

Coagulation Testing

When heparin sodium is administered in therapeutic amounts, its dosage should be regulated by frequent blood-coagulation tests. If the coagulation test is unduly prolonged or if hemorrhage occurs, heparin sodium should be discontinued promptly (see OVERDOSAGE).

Thrombocytopenia

Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0% to 30%. Mild thrombocytopenia (count greater than 100,000/mm³) may remain stable or reverse even if heparin is continued. However, thrombocytopenia of any degree should be monitored closely. If the

count falls below 100,000/mm³ or if recurrent thrombosis develops (see PRECAUTIONS; White–Clot Syndrome), the heparin product should be discontinued. If continued heparin therapy is essential, administration of heparin from a different organ source can be reinstituted with caution.

Miscellaneous

The 5,000 USP heparin units/mL product contains benzyl alcohol as a preservative. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

PRECAUTIONS

General

White–Clot Syndrome

It has been reported that patients on heparin may develop new thrombus formation in association with thrombocytopenia, resulting from irreversible aggregation of platelets induced by heparin, the so-called "white–clot syndrome". The process may lead to severe thromboembolic complications like skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke, and possibly death. Therefore, heparin administration should be promptly discontinued if a patient develops new thrombosis in association with thrombocytopenia.

Heparin Resistance

Increased resistance to heparin is frequently encountered in fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer, and in postsurgical patients.

Increased Risk in Older Women

A higher incidence of bleeding has been reported in women over 60 years of age.

Laboratory Tests

Periodic platelet counts, hematocrits, and tests for occult blood in stool are recommended during the entire course of heparin therapy, regardless of the route of administration (see DOSAGE AND ADMINISTRATION).

Drug Interactions

Oral Anticoagulants

Heparin sodium may prolong the one-stage prothrombin time. Therefore, when heparin sodium is given with dicumarol or warfarin sodium, a period of at least 5 hours after the last intravenous dose or 24 hours after the last subcutaneous dose should elapse before blood is drawn if a valid prothrombin time is to be obtained.

Platelet Inhibitors

Drugs such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, hydroxychloroquine, and others that interfere with platelet-aggregation reactions (the main hemostatic defense of heparinized patients) may induce bleeding and should be used with caution in patients receiving heparin sodium.

Other Interactions

Digitalis, tetracyclines, nicotine, or antihistamines may partially counteract the anticoagulant action of heparin sodium.

Intravenous nitroglycerin administered to heparinized patients may result in a decrease of the partial thromboplastin time with subsequent rebound effect upon discontinuation of nitroglycerin. Careful monitoring of partial thromboplastin time and adjustment of heparin dosage are recommended during coadministration of heparin and intravenous nitroglycerin.

When clinical circumstances require reversal of heparinization, consult the labeling of Protamine Sulfate Injection, USP.

Drug/Laboratory Test Interactions

Hyperaminotransferasemia

Significant elevations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT]) levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin. Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, rises that might be caused by drugs (like heparin) should be interpreted with caution.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of heparin. Also, no reproduction studies in animals have been performed concerning mutagenesis or impairment of fertility.

Pregnancy

Teratogenic Effects — Pregnancy Category C

Animal reproduction studies have not been conducted with heparin sodium. It is also not known whether heparin sodium can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Heparin sodium should be given to a pregnant woman only if clearly needed.

Nonteratogenic Effects

Heparin does not cross the placental barrier.

Nursing Mothers

Heparin is not excreted in human milk.

Pediatric Use

See DOSAGE AND ADMINISTRATION.

ADVERSE REACTIONS

Hemorrhage

Hemorrhage is the chief complication that may result from heparin therapy (see WARNINGS). An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug (see OVERDOSAGE). It should be appreciated that gastrointestinal or urinary-tract bleeding during anticoagulant therapy may indicate the presence of an underlying occult lesion. Bleeding can occur at any site but certain specific hemorrhagic complications may be difficult to detect:

a. Adrenal hemorrhage, with resultant acute adrenal insufficiency, has occurred during anticoagulant therapy. Therefore, such treatment should be discontinued in patients who develop signs and symptoms of acute adrenal hemorrhage and insufficiency. Initiation of corrective therapy should not depend on laboratory confirmation of the diagnosis, since any delay in an acute situation may result in the patient's death.

b. Ovarian (corpus luteum) hemorrhage developed in a number of women of reproductive age receiving short- or long-term anticoagulant therapy. This complication, if unrecognized, may be fatal.

c. Retroperitoneal hemorrhage.

Local Irritation

Local irritation, erythema, mild pain, hematoma, or ulceration may follow deep, subcutaneous (intrafat) injection of heparin sodium. These complications are much more common after intramuscular use, and such use is not recommended.

Hypersensitivity

Generalized hypersensitivity reactions have been reported, with chills, fever, and urticaria as the most usual manifestations, and asthma, rhinitis, lacrimation, headache, nausea and vomiting, and anaphylactoid reactions, including shock, occurring more rarely. Itching and burning, especially on the plantar side of the feet, may occur attributed to allergic vasospastic reactions. Whether these are, in fact, identical to the thrombocytopenia associated complications remains to be determined.

Miscellaneous

Osteoporosis following long-term administration of high doses of heparin, cutaneous necrosis after systemic administration, suppression of aldosterone synthesis, delayed transient alopecia, priapism, and rebound hyperlipemia on discontinuation of heparin sodium have also been reported.

Significant elevations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT]) levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin.

OVERDOSAGE

Symptoms

Bleeding is the chief sign of heparin overdosage. Nosebleeds, blood in urine, or tarry stools may be noted as the first sign of bleeding. Easy bruising or petechial formations may precede frank bleeding.

Treatment

Neutralization of heparin effect.

When clinical circumstances (bleeding) require reversal of heparinization, protamine sulfate (1% solution) by slow intravenous injection will neutralize heparin sodium. No more than 50 mg should be administered, very slowly, in any 10-minute period. Each mg of protamine sulfate neutralizes approximately 100 USP heparin units. The amount of protamine required decreases over time as heparin is metabolized. Although the metabolism of heparin is complex, it may, for the purpose of choosing a protamine dose, be assumed to have a half-life of about 1/2 hour after intravenous injection.

Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported, the drug should be given only when resuscitation techniques and treatment of anaphylactoid shock are readily available.

For additional information, consult the labeling of Protamine Sulfate Injection, USP products.

DOSAGE AND ADMINISTRATION

When heparin is added to an infusion solution for continuous intravenous administration, the container should be inverted at least six times to insure adequate mixing and prevent pooling of the heparin in the solution.

Heparin sodium is not effective by oral administration and should be given by intermittent intravenous injection, intravenous infusion, or deep subcutaneous (intrafat, i.e., above the iliac crest or abdominal fat layer) injection. *The intramuscular route of administration should be avoided because of the frequent occurrence of hematoma at the injection site.*

The dosage of heparin sodium should be adjusted according to the patient's coagulation-test results. When heparin is given by continuous intravenous infusion, the coagulation time should be determined approximately every 4 hours in the early stages of treatment. When the drug is administered intermittently by intravenous injection, coagulation tests should be performed before each injection during the early stages of treatment and at appropriate intervals thereafter. Dosage is considered adequate when the activated partial thromboplastin time (APTT) is 1.5 to 2 times normal or when the whole blood clotting time is elevated approximately 2.5 to 3 times the control value. After deep, subcutaneous (intrafat) injections, tests for adequacy of dosage are best performed on samples drawn 4 to 6 hours after the injections.

Periodic platelet counts, hematocrits, and tests for occult blood in stool are recommended during the entire course of heparin therapy, regardless of the route of administration.

Converting to Oral Anticoagulant

When an oral anticoagulant of the coumarin or similar type is to be begun in patients already receiving heparin sodium, baseline and subsequent tests of prothrombin activity must be determined at a time when heparin activity is too low to affect the prothrombin time. This is about 5 hours after the last IV bolus and 24 hours after the last subcutaneous dose. If continuous IV heparin infusion is used, prothrombin time can usually be measured at any time. In converting from heparin to an oral anticoagulant, the dose of the oral anticoagulant should be the usual initial amount, and thereafter prothrombin time should be determined at the usual intervals. To ensure continuous anticoagulation, it is advisable to continue full heparin therapy for several days after the prothrombin time has reached the therapeutic range. Heparin therapy may then be discontinued without tapering.

Therapeutic Anticoagulant Effect With Full-Dose Heparin

Although dosage must be adjusted for the individual patient according to the results of suitable laboratory tests, the following dosage schedules may be used as guidelines:

METHOD OF ADMINISTRATION	FREQUENCY	RECOMMENDED DOSE [Based on 150 lb (68 kg) patient]
Deep, Subcutaneous (Intrafat) Injection	Initial Dose	5,000 units by IV injection followed by 10,000 to 20,000 units of a concentrated solution, subcutaneously
A different site should be used for each injection to prevent the development of massive hematoma.	Every 8 hours or	8,000 to 10,000 units of a concentrated solution
	Every 12 hours	15,000 to 20,000 units of a concentrated solution
Intermittent, Intravenous Injection	Initial Dose	10,000 units, either undiluted or in 50 mL or 100 mL of Sodium Chloride Injection, USP, 0.9%
	Every 4 to 6 hours	5,000 to 10,000 units, either undiluted or in 50 mL to 100 mL of Sodium Chloride Injection, USP, 0.9%
Intravenous Infusion	Initial Dose	5,000 units by IV injection
	Continuous	20,000 to 40,000 units/24 hours in 1,000 mL of Sodium Chloride Injection, USP, 0.9% (or in any compatible solution) for infusion

Pediatric Use

Follow recommendations of appropriate pediatric reference texts. In general, the following dosage schedule may be used as a guideline:

Heparin sodium may prolong the one-stage prothrombin time. Therefore, when heparin sodium is given with dicumarol or warfarin sodium, a period of at least 5 hours after the last intravenous dose or 24 hours after the last subcutaneous dose should elapse before blood is drawn if a valid prothrombin time is to be obtained.

Platelet Inhibitors

Drugs such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, hydroxychloroquine, and others that interfere with platelet-aggregation reactions (the main hemostatic defense of heparinized patients) may induce bleeding and should be used with caution in patients receiving heparin sodium.

Other Interactions

Digitalis, tetracyclines, nicotine, or antihistamines may partially counteract the anticoagulant action of heparin sodium.

Intravenous nitroglycerin administered to heparinized patients may result in a decrease of the partial thromboplastin time with subsequent rebound effect upon discontinuation of nitroglycerin. Careful monitoring of partial thromboplastin time and adjustment of heparin dosage are recommended during coadministration of heparin and intravenous nitroglycerin.

When clinical circumstances require reversal of heparinization, consult the labeling of Protamine Sulfate Injection, USP.

Drug/Laboratory Test Interactions

Hyperaminotransferasemia

Significant elevations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT]) levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin. Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, rises that might be caused by drugs (like heparin) should be interpreted with caution.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of heparin. Also, no reproduction studies in animals have been performed concerning mutagenesis or impairment of fertility.

Pregnancy

Teratogenic Effects — Pregnancy Category C

Animal reproduction studies have not been conducted with heparin sodium. It is also not known whether heparin sodium can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Heparin sodium should be given to a pregnant woman only if clearly needed.

Nonteratogenic Effects

Heparin does not cross the placental barrier.

Nursing Mothers

Heparin is not excreted in human milk.

Pediatric Use

See DOSAGE AND ADMINISTRATION.

ADVERSE REACTIONS

Hemorrhage

Hemorrhage is the chief complication that may result from heparin therapy (see WARNINGS). An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug (see OVERDOSAGE). It should be appreciated that gastrointestinal or urinary-tract bleeding during anticoagulant therapy may indicate the presence of an underlying occult lesion. Bleeding can occur at any site but certain specific hemorrhagic complications may be difficult to detect:

a. Adrenal hemorrhage, with resultant acute adrenal insufficiency, has occurred during anticoagulant therapy. Therefore, such treatment should be discontinued in patients who develop signs and symptoms of acute adrenal hemorrhage and insufficiency. Initiation of corrective therapy should not depend on laboratory confirmation of the diagnosis, since any delay in an acute situation may result in the patient's death.

b. Ovarian (corpus luteum) hemorrhage developed in a number of women of reproductive age receiving short- or long-term anticoagulant therapy. This complication, if unrecognized, may be fatal.

c. Retroperitoneal hemorrhage.

Local Irritation

Local irritation, erythema, mild pain, hematoma, or ulceration may follow deep, subcutaneous (intrafat) injection of heparin sodium. These complications are much more common after intramuscular use, and such use is not recommended.

Hypersensitivity

Generalized hypersensitivity reactions have been reported, with chills, fever, and urticaria as the most usual manifestations, and asthma, rhinitis, lacrimation, headache, nausea and vomiting, and anaphylactoid reactions, including shock, occurring more rarely. Itching and burning, especially on the plantar side of the feet, may occur.

Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0% to 30%. While often mild and of no obvious clinical significance, such thrombocytopenia can be accompanied by severe thromboembolic complications, such as skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke, and possibly death. (See WARNINGS and PRECAUTIONS.)

Certain episodes of painful, ischemic and cyanosed limbs have in the past been

products.

DOSAGE AND ADMINISTRATION

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Pediatric Use

Follow recommendations of appropriate pediatric reference texts. In general, the following dosage schedule may be used as a guideline:

Initial Dose: 50 units/kg (IV drip)

Maintenance Dose: 100 units/kg (IV drip) every four hours, or 20,000 units/m^2/24 hours continuously.

Surgery of the Heart and Blood Vessels

Patients undergoing total body perfusion for open-heart surgery should receive an initial dose of not less than 150 units of heparin sodium per kilogram of body weight.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040095

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 3

2. ANDA 40-095

3. NAME AND ADDRESS OF APPLICANT
Sanofi Winthrop Inc.
90 Park Avenue
New York, NY 10016

4. LEGAL BASIS FOR ANDA SUBMISSION
Generic version of Wyeth Ayerst's Heparin Sodium Injection, USP (NDA 17-007).

Patent certification and exclusivity statement provided (pages 14 and 15).

5. SUPPLEMENT(s) N/A

6. DRUG NAME
Heparin Sodium Injection USP

7. PROPRIETARY NAME
N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR Original ANDA

9. AMENDMENTS AND OTHER DATES

Firm		FDA	
Orig. submission	12/17/93	ANDA acknowledgement letter	01/27/94
		Labeling review	03/22/94
		Bio review	03/16/94
		Micro review	04/13/94
		Deficiency letter	04/29/94
New correspondence	09/30/94		
New correspondence	09/30/94		
Amendment (major)	12/14/94	Labeling review	01/04/95
		Micro review	03/20/95
		Deficiency letter	04/28/95
New correspondence	03/02/95	Ownership letter	07/13/95
Amendment (major)	05/17/96	Micro review	06/07/96
		Labeling review	06/13/96

This review covers amendment dated 5/17/96.

10. PHARMACOLOGICAL CATEGORY
Anti-coagulant

11. Rx or OTC
℞

- Continuous -

12. RELATED DMF(s)

(b)4 - Confidential Business

13. DOSAGE FORM
Injection

14. STRENGTH(S)
10,000 Units/mL

15. CHEMICAL NAME AND STRUCTURE **Satisfactory -**
(1) α-L-iduronic acid 2-sulfate, (2) 2-deoxy-2-sulfamino-α-D-glucose 6-sulfate, (3) ß-D-glucuronic acid, (4) 2-acetamido-2-deoxy-α-D-glucose, and (5) α-L-iduronic acid. These sugars are present in decreasing amounts, usually in the order (2)>(1)>(4)>(3)>(5), and are joined by glycosidic linkages, forming polymers of varying sizes. Official USP 23 drug substance and drug product (USP 23, pages 736-738).

16. RECORDS AND REPORTS None

17. COMMENTS N/A

18. CONCLUSIONS AND RECOMMENDATIONS

APPROVE

19. REVIEWER:
Raymond Brown

DATE COMPLETED:
June 28, 1996

/S/

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040095

BIOEQUIVALENCE REVIEW(S)

MAR 16 1994

Heparin Sodium
10,000 units/mL 1 mL fill in 2 mL Vial
ANDA # 40-095
Reviewer: Man M. Kochhar
40095W.D93

Sterling Winthrop Inc.
New York, N.Y.
Submission Date:
December 17, 1993

Review of a Waiver Request

The Firm has requested a waiver of in vivo bioequivalence study for its heparin sodium 10,000 units/mL, 1 mL fill in 2 mL vial injections based upon 21 CFR 320.22 (b) (1).

Comparative Formulation

Ingredients	Sterling Winthrop Amount/mL	Wyeth Amount/mL
Heparin Sodium	10,000 units	10,000 units
Benzyl Alcohol	----	10 mg
Water for injection, USP(q.s. ad)	1.00 mL	1.00 mL
Hydrochloric Acid (q.s) or Sodium Hydroxide (q.s)	pH 5.0 - 7.5	pH 5.0 - 7.5

Deficiency: None

Comments:

1. The formulation of the test product and the innovator product heparin sodium (Wyeth) is similar in concentration of active and inactive ingredients except benzyl alcohol. The test product does not contain benzyl alcohol. The benzyl alcohol serves as a preservative and the test product is intended and labeled for single use, therefore, the use of preservative is not warranted. Benzyl alcohol does not affect the bioavailability of the product.

2. The dosage form, route of administration (intravenous), strength (10,000 units/mL) and labeling of the test drug product are identical to those of the innovator product, heparin sodium (Wyeth). The dosages of the test and reference products are same.

3. From the bioequivalence point of view, the waiver of in vivo bioequivalence study requirement should be granted based on 21 CFR 320.22 (b)(1). The batch size is 50 and 500 liters.

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Sterling Winthrop on its Heparin Sodium 10,000 units/mL, 1 mL fill in 2 mL vial injection falls under 21 CFR 320.22 (b)(1) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for 10,000 units/mL, 1 mL fill in 2 mL vial injection of the test product is granted.

From the bioequivalence point of view, the Division of Bioequivalence deems the test injection of Heparin Sodium 10,000 units/mL, 1 mL fill in 2 mL vial to be bioequivalent to Heparin Sodium, 10,000 units/mL, 1 mL manufactured by Wyeth.

The firm should be informed of the recommendation.

/S/

Man M. Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/

MMKochhar/mmk/2-14-94/40095

cc: ANDA # 40-095 original, HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Kochhar), Drug File, Division File.